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FUNCTIONAL ASSESSMENT OF LASER IRRADIATION

ANNUAL REPORT

DAVID O. ROBBINS, Ph.D.

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FOREWORD

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978).

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INTRODUCTION

The development and use of the laser both in the field and laboratory has grown significantly over the past several decades since its discovery in 1960. Today, over 150 different types of laser systems have been developed and further proliferation of lasers is almost certain. These coherent light sources not only differ in output power and wavelength but also the manner in which the light is delivered. Older and less powerful systems deliver a steady stream of photons while newer systems emit extremely powerful, short duration pulses.

This light form, both in its inherent properties and potential power levels, poses possible health hazards not common with other light sources. As a consequence users and others who might be exposed to laser light need to be protected from possible damage due to overabsorption. Damage to biological tissue can result from a brief, single exposure to a laser beam or from multiple exposures to power levels which initially produce no observable consequences. Any bodily organ which can absorb the incident wavelength has the potential of being damaged depending upon its own threshold for damage, the amount of energy absorbed, and the dissipation of energy over time. Since the eye is designed to absorb incident light by nature, it is especially vulnerable to morphological alterations as a result of even brief exposures to laser light. Dependent upon output energy and wavelength, damage can be restricted primarily to the cornea or to the electrically photosensitive retina. Damage to the cornea can be extremely painful and can alter the transmission properties of the cornea. Damage at the retinal level can produce either temporary or permanent changes in the ability of the photoreceptor to absorb light or its ability to propagate neural signals

throughout the retina and beyond.

Associated with these morphological and physiological alterations are deficits in visual sensitivity including changes in visual resolution and spectral and contrast sensitivity. For the soldier, even temporary visual impairment could jeopardize the individual's ability to complete a visual-motor response and thereby imperil himself or that of his fellow soldiers in the successful completion of a mission. Hence, establishing safe operating guidelines, developing protective devices against accidental exposure, and determining the visual consequences of retina exposure must remain a high priority in any laser research program.

Thresholds for ocular damage can be determined by traditional morphological means (fundoscopically or histologically) or can be defined in terms of changes in the visual sensitivity of the organism exposed as determined either behaviorally or through electrophysiological analyses of retinal function. In some ways the latter criteria may ultimately be the most important in determining the ability of an exposed soldier to successfully complete a visually-guided motor response. Furthermore, legal liability for treatment and provisions for medical disability will not be determined by the presence or absence of tissue alterations alone but by the presence of any perceived change in the ability of the person to perform visually.

Technological advances in other fields such as histology and electrophysiology have greatly improved the analytical methodology for assessing fine retinal damage as a result of light overstimulation. Associated with these methodological changes has been the demonstration that moderate as well as intense light can produce permanent changes in retinal morphology (1, 2, 3). But predicted and observed damage thresholds became inconsistent, in part due to different assessment techniques with varying

sensitivities for defining damage thresholds. Additional inconsistencies were the result of growing diversities within the delivery systems and wavelengths of new laser devices. For example, histopathological examination reveals retinal damage at lower exposure levels than are observed by ophthalmological examination alone especially when the area of retinal involvement is restricted. On the other hand, functional criteria are often considered to be the most sensitive, especially when considering wide field stimulation since subtle enzyme and photochemical changes as well as minute structural changes can cause shifts in visual sensitivity in cases where observable morphological disruptions are difficult or impossible to detect.

Even with functional criteria, however, thresholds for permanent shifts in visual sensitivity have varied depending upon the visual task used to assess function. Changes in the luminance, wavelength, and contrast of test targets have yielded various damage thresholds but most are considerably lower than those derived under maximum achromatic photopic conditions and considerably below those derived using traditional morphological criteria. Relatively recent improvements in techniques for functional assessment (4) have even further lowered the functional threshold for acuity and provided the opportunity for the examination of the transitional zone between temporary and permanent shifts in visual acuity. This method eliminated the time delay for recovery from the anesthetic which was a part of all previous behavioral studies and which had prevented any postexposure testing for at least the first 24 hours. This restriction in previous behavioral methodologies also eliminated any possibility for the examination of changes in sensitivity during the early course of recovery and/or repair. The present report utilizes this improved method for exposing awake, task-oriented rhesus monkeys and examines both the immediate and long term shifts in visual sensitivity following laser exposure.

There have been no direct systematic studies to examine any differential effect thermal and/or mechanical damage mechanisms may have on human visual sensitivity. Furthermore, due to the nature of laser safety investigations, the use of human subjects poses serious methodological and ethical problems that are not easily resolved. As a consequence, intentional human laser exposure has been limited to those eyes that suffer severe retinopathies or eyes which are slated for enucleation. The degradation of such eyes as well as the usual medical urgency for removal of the eye prevents the performance of complete postexposure testing on these subjects (5,6). Therefore, for behavioral studies, a suitable animal model had to be found.

The selection of the rhesus monkey was based on the similarity of its retinal anatomy and physiology to that of the human and its comparable visual sensitivity. In spite of some small discrepancies, both the visual performance and retinal anatomy of the two species are remarkably similar, making the rhesus an excellent human prototype for these type of investigations. Furthermore, the position of this animal on the phylogenetic scale and its implied superior intellectual abilities lead one to assume that the strategies employed by these animals to compensate for any lost visual function may not be significantly different from those employed by their human counterparts especially when considering the motivational level under which these subjects are tested.

As previously mentioned, functional studies are important in determining safety standards for laser irradiation since morphological criteria alone tell little about the degradation of visual performance accompanying any such damage. Furthermore, prior to the current effort, virtually no exploration of exposures levels at or slightly below the transition from temporary to permanent visual losses has been conducted since no technique was available to expose an awake, task-oriented animal. Instead, early behavioral studies were

restricted to the evaluation of severe retinal morphological disruptions of the rhesus fovea (7, 8, 9, 10). The effects of these foveal irradiation levels were usually permanent, producing impairment in visual acuity ranging from 40% to 80% of pre-exposure levels. In these previous studies, anesthesia was required for the placement of retinal lesions, thereby eliminating any possibility of immediate postexposure acuity measurements for at least 24 hrs. The inability of these former studies to measure transient changes in visual acuity at threshold and subthreshold energy levels, as well as a means to follow the initial phases of deficits elicited by suprathreshold energy levels, was a serious limitation. During the course of the current research effort, we have examined the immediate as well as the long term effects of single and repeated exposure to Argon (514 nm), HeNe (633 nm), and Krypton (647 nm) lasers. Various parameters of the exposure have been manipulated including energy density, duration, spot size, and position on the retina. Likewise, in an attempt to assess vision under a variety of photopic and scotopic viewing conditions, we have varied the background luminance, wavelength, and contrast of acuity targets of varying sizes and orientations. Although much work has been done in this area, there is still much to be determined not only to protect human observers from accidental exposure but also to prevent underutilization of lasers because of unrealistic restrictions placed upon its employment. In addition, as new laser systems are produced, new standards have to be developed to account for any changes in output energies, wavelengths, and/or durations. Further, the long term consequences of repeated exposures are less delineated than are those that result from the single exposure condition.

METHODS

A detailed description of the methods used to expose, awake, task oriented rhesus monkeys has been presented elsewhere (11) and will be only briefly described here. This method has reliably produced foveal exposures in conscious animals and has allowed for the measurement of shifts in acuity and in contrast and chromatic sensitivity prior to and immediately following exposure.

SUBJECTS Male rhesus monkeys ages 2 through 8 and weighing 8 to 10 lbs. were used as experimental subjects. All animals were examined fundoscopically prior to exposure and, together with pre-exposure measurements of visual acuity, revealed no refractory errors or morphological abnormalities in their retinae.

All subjects were housed individually in standard primate cages and were free to move about in their home environment. Animals were fitted with a custom, light-weight, plastic neck collar for capturing purposes. The home environment was enriched with a variety of activities including TV, radio and play activities during the daylight hours. Light/dark cycles as well as temperature and humidity was controlled. The animals' diets and liquid intake were monitored and animals were under veterinarian supervision when housed in the laboratory. Each animal was routinely TB tested.

Apparatus. A restraint device was used during acuity testing to assure the animal's correct line of fixation and distance from the viewing screen. Restraint during exposure was necessary for proper placement of exposures on the central fovea since the animals were not anesthetized during this experiment. Historically, when the experimental paradigm requires temporary restraint of the animal on a daily basis, chronic restraint devices such as primate chairs have been employed. Since the restraint period for this

experiment extended over a period of months, such a procedure was judged to be detrimental to both the welfare of the animal and the purpose of the

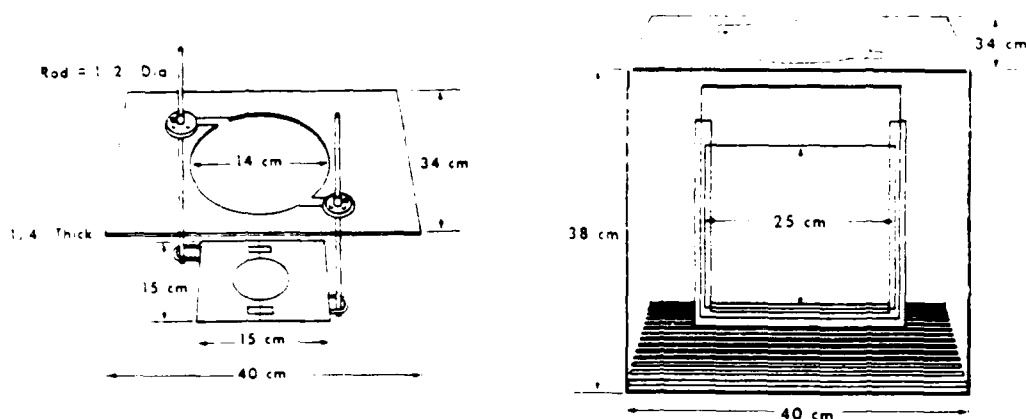


Figure 1. Diagram of the Plexiglas restraint device used during laser exposure and acuity testing. The overall dimensions of the cage, 40 w x 38 h x 34 d cm, readily accommodate rhesus monkeys of various sizes. The box was constructed of 3/8" Plexiglas with 1/2" aluminum rods forming the floor. Diagram of the collar, worn by the rhesus monkey, against the top panel of the restraint cage is shown in the diagram to the left. The poles are then secured with lattice frame base plates (hooks on the pole are not shown). The diagram on the right shows the Plexiglas door which when abutted against the door of the home cage, allows the animal to enter or exist. The top of the device contained a 14 cm diameter hole through which the animal's head could be projected. On either side of this hole, slots were cut through which rods with hooks could be inserted and attached to the rings on the animal's collar. These rods were used to draw the animal's collar up against the top of the restraint cage and assure fixation of the animal's neck. The animal was then custom fitted with a Plexiglas helmet which minimized head movements. An opaque facemask with adjustable iris diaphragms was aligned with the animal's pupils and, once inside the test chamber, positioned with the viewing screen so eye position could be tightly controlled. Small, voluntary head or eye movements by the animal would block the animal's line of sight with the viewing screen and could result in the animal being negatively reinforced for incorrect detections. As a consequence, subjects learned rather quickly to remain fixed in position once aligned with the screen. During the setup procedures, the animals were also positively reinforced with either fruit or juice for cooperative behavior and the animals were always physically separated from the experimenter preventing accidental injury to either party.

experiment. On the other hand, daily administration of anesthesia was judged to be detrimental to the general health and so a behavioral technique was developed for transferring animals from their home cage to the experimental cubicle. Often the animal in this situation is uncooperative either because of fear or adverse conditioning.

In our procedure, the animals were conditioned to enter a specially designed squeeze device which easily converted to a temporary restraint-type chair. Prior to training the animals were custom fitted with a 15 x 15 cm Plexiglas collar. Ketamine was used to temporarily immobilize the animal during fitting. Our animals completely adapted to wearing these collars within several hours following recovery from the anesthetic and we observed no health problems or chafing in animals chronically wearing these collars over a period of several years.

A description and diagram of the restraint device is shown in Figure 1. The entire restraint device was mounted on a hydraulic lift platform attached to a mobile cart. This portable cart allowed easy positioning of the device against the home cage and within the experimental chamber when transferring and transporting the animal for testing.

All laser exposures and pre- and postexposure assessments of visual acuity were made in the same light-tight, sound attenuated chamber. A white noise generator was used to mask sounds generated by the experimental equipment located in a nearby room. The chamber measured 70" x 26" and contained mounting brackets to lock the portable restraint device in position once proper alignment with the viewing screen was assured. Mounted on the far wall was a rear projection screen subtending 3 deg at a distance of 1 m from the animal's pupil. Two carousel projectors, positioned outside the experimental chamber, served as the source for image projection and the background of the viewing screen. Luminances and wavelengths of both the

viewing background and test targets were determined independently by placement of neutral density and interference filters in the light paths. Both the image and background carousel projectors were programmable and were internally able to read a variety of coded slides. Acuity was measured using standard Landolt rings and square-wave gratings. These slides were photographically produced on Kodak high contrast film (Kodalith) and were photographically reduced to produce different size targets. The Landolt rings were black on a clear background. The thickness of the Landolt rings and the width of the gap that formed the critical detail were always $1/5$ of the diameter of the ring. The size of the gap could be varied from 0.25 to 30 min of visual angle in equal steps. The position and orientation of the gap in the Landolt rings was always in the same location on the screen. Except for the screen, the test chamber was entirely dark. The presentation of slides, recording of the animal's responses, and consequences for the behavior were under the control of a LVE/BRS Interact System and Data General Nova 3 microprocessor. An Apple IIe microprocessor was also used for on-line data analysis, display, and storage.

Discrimination Task. Animals were trained using an avoidance paradigm to press a lever in the presence of a Landolt "C" and not to respond in the presence of a gapless Landolt ring. Failure of the animal to press the lever in the presence of a Landolt "C" (defined as "miss") or lever pressing in the presence of gapless rings (defined as a "false positive") resulted in the presentation of a discriminative tone and, on a variable reinforcement schedule, a brief, weak electrical shock. The shock was obtained from the secondary of a high-tension coil by discharging a capacitor into the primary, and was annoying but not highly painful as the authors can testify from experience. Swinnen, Brady & Powell (12) have concluded that because of its short duration this type of shock is safer for rhesus than conventional

electric shock. The use of negative reinforcement during testing was necessary in order to consistently maintain the animal's vigilance during the course of testing and especially immediately following laser exposure. A well trained and vigilant animal could avoid shock altogether.

Following shaping, threshold acuity testing was derived using a modification of the von Bekesy tracking technique (13). In this technique, if the subject correctly detected the Landolt ring by pressing a lever (hit), a discriminable tone was presented and the next series of Landolt rings and gapless rings was 20% smaller. Incorrect detection of the Landolt ring (miss) resulted in a different discriminable tone, the possibility of a brief shock on either a fixed or variable ratio schedule, and the presentation of rings 20% larger. To discourage the animal from responding indiscriminately to all rings, a third discriminable tone was presented immediately following lever responses to gapless rings (false positive) and, on a fixed ratio schedule, the animal received a brief shock for these incorrect responses. The number of false positive responses was always low in trained animals (less than 10%). Using this paradigm, the size of the threshold target was always at the animal's threshold thereby eliminating time spent testing targets either significantly above or below threshold. The test objects were typically presented in sets of four rings that were of equal diameter. Three of the rings in each set were gapless, while the fourth was a Landolt "C" that appeared in a random position within the set. Each ring was projected for 2 sec. and there was a 1 sec. dark interval between successive rings. The size of the test series was shifted only on responses to Landolt "C" rings and not to gapless rings. Baseline means, variability, and false positive responses in both the exposed and control eye were monitored daily throughout the experiment.

The luminance, wavelength, and contrast of the background upon which the

darkened test target was projected could be varied by a second projector to measure threshold acuity under a variety of viewing conditions. All measurements were made under monocular conditions and after the animal had adapted to the luminance level of the screen.

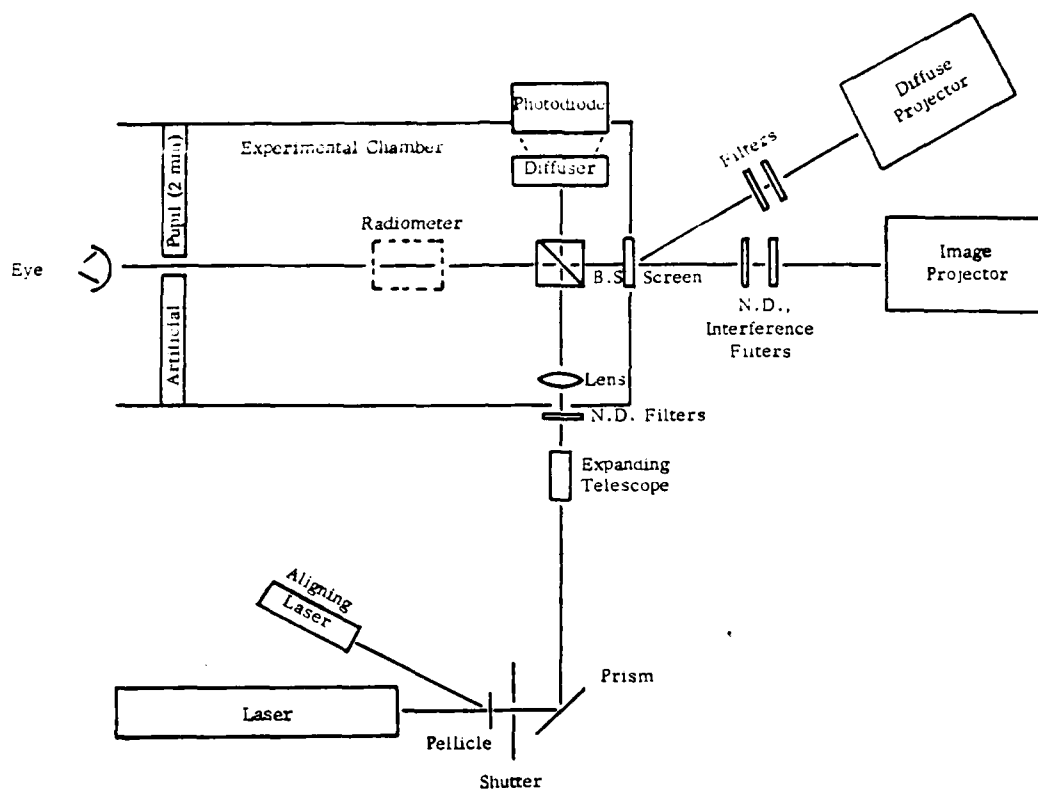


Figure 2. Diagram of the laser and image optical system. Various laser systems have been used as exposure sources including HeNe (632.8 nm), Krypton (647 nm) Argon (514.5 nm), and Nd/YAG (532 nm). The position and the size of the beam on the retina was controlled by the expanding telescope and the converging lens used to present the spot in Maxwellian view. An electronic shutter controlled exposure duration for CW lasers. Discriminable stimuli were presented by a programmable Kodak carousel projector while a second programmable projector was used to vary the contrast of the darkened target against a light background. The animal within a restraint apparatus was positioned behind a wall such that it could monocularly view the screen and discriminanda only by looking through a small fixed, artificial pupil.

Laser System. A 4.0 W CW Argon laser (Spectra Physics, Model 165/265) served as the laser source. A small HeNe laser is used for aligning purposes. A diagram of the optical system is shown in Figure 2. The entire laser system, with the exception of a beam splitter and focusing lens, was mounted outside the experimental chamber. The "raw" laser beam passed first through several neutral density filters for attenuation and then through a manual safety shutter. The attenuated beam was then directed through an electronic shutter which produced a calibrated exposure of between 1 and 100 msec when triggered electronically by the experimenter. The beam was then diverted by a 4.5 cm diameter front surface mirror and entered a beam expanding telescope which produced a collimated beam of adjustable diameter between 100 and 500 microns. When a minimal diameter spot (<50 microns) on the retina was presented, the expanding telescope was removed from the optical system. The expanded beam was then directed through a final focusing lens and a 5 x 10 cm coated pellicle beam splitter placed at the intersection of the diverging laser beam and the beam from the rear-projection, viewing screen. The converging beam then passed through a final 4 mm aperture positioned just in front of the animal's natural pupil.

Mounted on the opposite side of the beam splitter was a diffuser and ultrafast photodiode (HPA 4203). The output of this detector was displayed on a memory oscilloscope and was regularly calibrated against an EFF Model 580 Radiometer placed at the corneal plane. The power and pulse width of each laser exposure was measured and recorded.

Proper alignment of the laser beam with the animal's pupil was critical. The laser beam was presented to the animal coaxial with a line between the artificial pupil and the gap in a specified, threshold Landolt ring which subtended less than 1 minute of arc. For determinations of the line of sight, a 2 mm aperture was placed on the screen over the position of the gap in the

specified Landolt ring. A mirror, approximately 2 m behind the 4 mm artificial pupil was then adjusted until it was normal to the line of sight. With the converging lens removed, the beam splitter at the junction of the image and laser beams was then aligned so that the collimated beam from the laser past through the 4 mm aperture and was reflected off the mirror back onto itself and through the 2 mm aperture at the projection screen. Coaxial alignments with the line-of-sight were then verified by noting that the reflected beam passed through both apertures and back on itself without any loss. The focusing lens was then positioned such that the cornea was in the focal plane of the lens and so as not to change the alignment of the beam with the line-of-sight adjustment. Presenting the beam in Maxwellian view reduced the possibility that changes in pupil diameter or small lateral movements of the animal's head would affect the amount of light entering the eye.

This laser system was capable of presenting single-pulsed exposures ranging from less than 100 msec to greater than 10 min. In those instances where acute exposures were made, exposure durations of less than 100 msec were used to avoid the confounding effect of involuntary and voluntary eye movements away from the spot. Such movements would spread the irradiation over a larger retinal area than that produced by the optics of the laser system and the eye itself. Corneal power densities of greater than 2 W over a retinal area of from less than 50 microns to greater than 500 microns in diameter were possible. Within limits, the location of the exposure on the retina (on- or off-axis) could be varied by adjusting the position of the beam relative to the animal's point of fixation on the viewing screen.

Laser exposure. Prior to any laser exposure, stable acuity levels were established for each of the subjects' eyes. A criterion of, at minimum, 14 consecutive sessions of threshold measurements was used to establish a mean and standard deviation acuity level for a number of different viewing

conditions. Acuity was derived using a variety of monochromatic and achromatic backgrounds under different luminance and contrast conditions.

Prior to each exposure, pre-exposure acuity was derived for each eye during a 15 - 20 min test session. Failure of the animal to obtain a mean acuity within one standard deviation of his predetermined acuity level aborted the laser exposure. Session variability or increased false positive responding beyond a pre-established level also aborted the session. In cases where the animal did not achieve his pre-exposure baseline level in an eye which had previously been exposed, testing was continued to establish the parameters of the visual deficit.

All exposures were made while the subject was actively discriminating threshold Landolt rings. Postexposure testing began immediately after each exposure and continued until the animal was able to re-establish his baseline level or until the session was terminated due to time. The laser flash was triggered immediately after the animal correctly detected a specified threshold Landolt. In previous studies using closed circuit television, it has been observed that our animals maintain fixation on the critical feature of the target for seconds following responding and until reinforced either with the discriminable tone or shock. No exposures were made following incorrect detections of threshold targets or following correct detections during the final 1 sec of the trial. Using this procedure immediate and significant downward shifts in acuity were noted in over 75% of the exposures presented. In those cases where no such downward shifts in acuity were noted, it is possible that involuntary or pre-established voluntary eye movements may have lead to exposures in the peripheral regions of the retina. Given the nature of our acuity task, exposure of this region of the retina would not have been difficult to detect. Control or sham exposures with the laser beam blocked at the point of the safety shutter tested for any factors within the

procedure which might change the animal's expectancy and response criterion.

Typically, only one exposure was made per session and in cases where the animal failed to return to his pre-exposure level during the exposure session, no exposures were made in subsequent sessions until a new baseline acuity level was established. At each power density, a repeated design was employed for each of the different types of viewing conditions employed. The order of viewing conditions under which exposures were made was random while the order of laser power densities presented was fixed, beginning first with the lowest and increasing in a stepwise order following completion of all viewing conditions. Postexposure testing was terminated after the animal had regained his pre-exposure acuity level for the given viewing condition or after 2 hrs of testing whichever came first. The animal's unexposed eye served as a control.

Statistical analyses of the data. Descriptive analyses of shifts in acuity were made for each exposure under each viewing condition. Since the number of exposed animals was relatively small, between subject analyses was limited and the majority of the analyses were made within subjects. Statistical comparisons were made of the changes in the degree and duration of the initial deficit as well as the total time for full recovery as a function of different exposure energies, durations, spot sizes, and wavelengths. Also examined was the effect the specific acuity task had on the magnitude and duration of the visual deficits. For each exposure paradigm, several different background conditions were examined under both photopic and scotopic viewing conditions.

The determination of the animal's performance level using the tracking technique was derived using the formula developed for the "Up and Down" procedure (14). The traditional means of presenting the data was to graph the average acuity maintained within each running two minutes following exposure.

This data could be graphed either in terms of the "Up and Down" procedure (raw data) or in terms of average visual acuity.

RESULTS

Complete baseline sensitivities were measured for each animal and for each eye prior to any laser exposure and were measured routinely throughout the period while the animal was receiving laser exposures. These baseline sensitivities often served as the reference for any observed deficit elicited by laser irradiation. Continual comparisons were made pre- and postexposure within the exposed eye and between this eye and the control eye which never received laser irradiation.

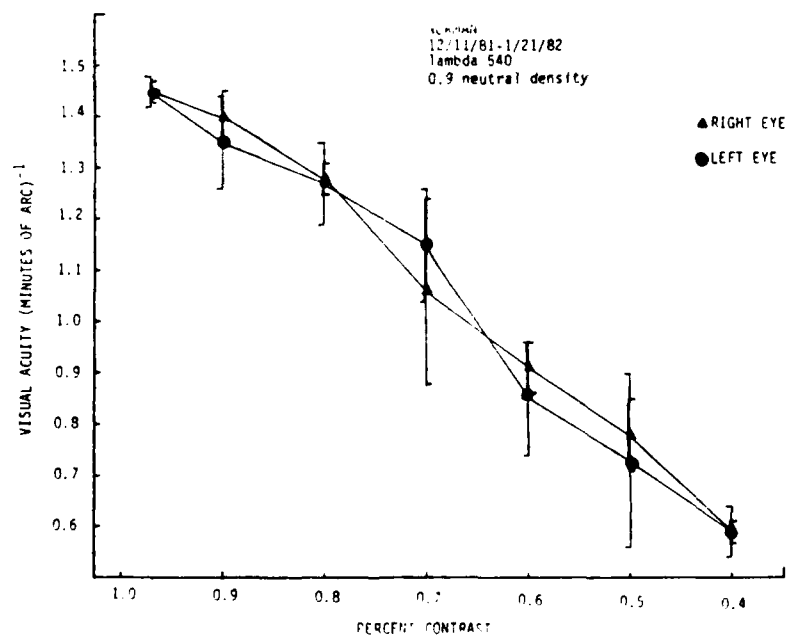


Figure 3. Visual acuity as a function of varying target contrasts for each eye prior to laser exposure. Contrast sensitivity was measured for each eye independently and each data point represents the mean acuity for several different test sessions. All backgrounds were equated for equal luminance and different contrast backgrounds were produced by a second diffusing light source. The vertical lines drawn through the data points represents ± 1 SD.

The baseline visual acuity of one animal for various contrast targets is shown in Figure 3. Varying contrasts were produced by flooding the rear projection screen with light from a second, diffusing projector which added light to both the background and the darkened Landolt ring. The overall luminance of the field was adjusted for equal energies.

A photopic spectral sensitivity curve for several animals is shown in Figure 4. As can be seen, peak sensitivity was at 540 nm although the shape of the curve was rather flat between 500 nm and 560 nm. Sensitivity appeared to drop off more expeditiously at the longer than the shorter wavelengths and this is generally characteristic of the long wavelength insensitivity of the rhesus especially at higher acuity criteria.

The initial effect of a brief laser exposure focused on the fovea is to produce an immediate shift in visual sensitivity followed by a gradual recovery in sensitivity over time provided the energy of the flash is below the threshold level for a permanent shift in acuity. A typical example of this effect on the ability of the animal to maintain maximum resolution on a photopic visual task is shown in Figure 5. In this figure recovery from a

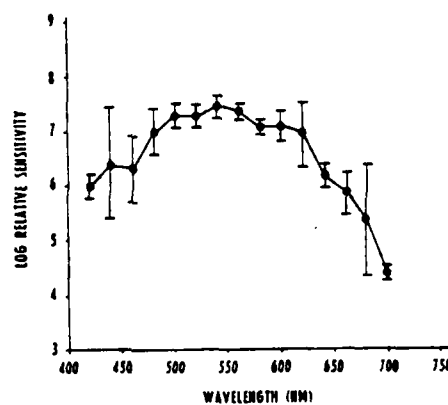


Figure 4. Spectral sensitivity curve for several rhesus monkeys. The vertical bars drawn through the data points represent ± 1 SD. Each data point represents the interpolated sensitivity corrected for quantal output derived from the mean regression equation of the combined individual intensity acuity functions for each wavelength.

brief, 100 msec flash of 632.8 nm light is shown. This figure represents the ability of one animal to track acuity immediately following exposure. Time, relative to exposure, is indicated on the abscissa. In the left-hand portion of the figure, acuity for a tracking task is shown for a 15 min period immediately preceding laser exposure. During this pre-exposure testing using a typical 4:1 ratio of gapless rings to Landolt C's, pre-exposure mean acuity was $1.25 \text{ (min of arc)}^{-1}$. Acuity was defined as the reciprocal of the visual angle subtended by the gap in a Landolt C at the 50% threshold point. Preceding the exposure, the S was transferred to a 2:1 ratio of gapless rings to Landolt C's and tested for an additional 2 min. The shift from 4:1 to a 2:1 ratio of gapless rings to Landolt "C"s was used to more rapidly access shifts in acuity and did not affect either the animal's response criteria or false positive rate. In this session, the animal was exposed to a single 100 msec laser flash following the correct detection of a $1.16 \text{ (min of arc)}^{-1}$ Landolt C which corresponded to the zero point on the abscissa of this figure. Immediately after exposure, the animal's acuity decreased to $0.51 \text{ (min of arc)}^{-1}$

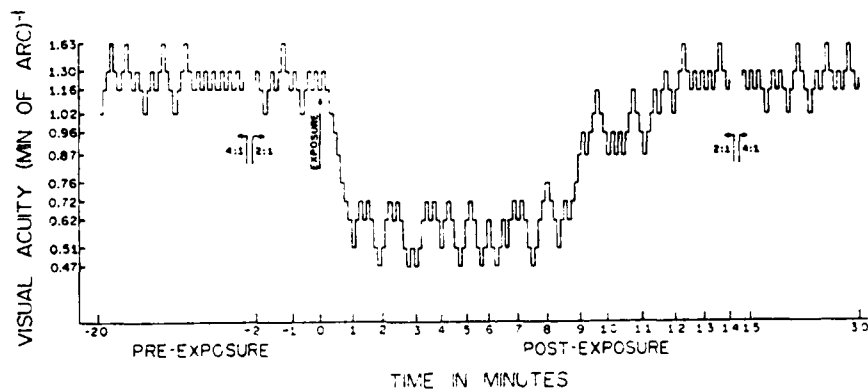


Figure 5. Sample raw data demonstrating the immediate drop in visual acuity immediately following laser irradiation. The ordinate indicates the various sizes of the gaps in presented Landolt rings and is plotted in reciprocal visual minutes of arc. This scale is measured in discrete steps, since the vertical excursions of the plot were taken from a nonlinear potentiometer mounted on the slide tray of a carousel which recorded tray position. The abscissa represents the presentation of the Landolt Cs; corresponding times (in minutes) for representative trials are indicated relative to exposure.

arc) ¹, which corresponds to an acuity deficit of 59% relative to its pre-exposure acuity. This visual deficit lasted 9 min before the subject's acuity gradually returned to its mean pre-exposure level. Total recovery from the initial deficit was complete in approximately 13 min. Threshold testing using the 2:1 ratio of gapless rings to Landolt Cs was continued for 3 additional minutes. The ratio of gapless rings to Landolt Cs was then shifted back to 4:1, and postexposure acuity measurements were extended for an additional 15 min. No permanent shift in pre- and postexposure acuity was found at the energy level (7 mW) used in this figure.

Using different laser systems including HeNe, Krypton, Argon, and Nd/YAG, we have explored the relationship between the magnitude and duration of any elicited deficits and the energy of the exposure. For descriptive purposes, the observed recovery process has been divided into two portions, an initial, rapid decline and eventual stabilization of acuity lasting anywhere from several minutes to hours followed by a gradual recovery to pre-exposure acuity levels for those energy densities where full recovery was observed. In those instances where recovery was not observed, typically the animal's postexposure acuity stabilized at the initial depressed acuity level often for several months before any further changes were noticed.

In previous studies we have noted that the magnitude of the initial deficit is related primarily to spot size rather than exposure energy, although exposure duration does affect the magnitude of the elicited acuity deficit. In this contract period we have continued to explore the relationship between spot size, exposure energy and duration on the magnitude of the initial deficit and the total time for full recovery. As previously reported, exposure energy was primarily related to recovery time while both spot size and exposure duration had more of an influence on the initial deficit.

Typically, immediately after exposure, acuity dropped to approximately 70% of its pre-exposure level and, depending upon the energy of the flash, remained at this depressed level for several minutes before gradually returning to its pre-exposure baseline level. During the course of the deficit, the animal appeared vigilant and did not alter his detection criteria as seen in an unchanged false alarm rate. Sham exposures in which the paradigm was identical but the laser flash was not delivered to the eye being tested yielded no change in visual performance or response criteria. An example of the type of deficit produced by an acute exposure is shown in Figure 6. The recovery time course observed here was significantly longer than that usually experienced for photopic bleaching but the energy level employed here was below that necessary to elicit a permanent functional alteration. In this figure the effects of two different power densities of Argon flashes (2.0 mW and 3.0 mW) are shown along with sham exposures where no laser flash was presented. In the sham condition, the size of the projected discriminanda was shifted to the animal's pre-established immediate postexposure acuity level and the animal's acuity was then followed until it returned to its pre-exposure baseline level. In our paradigm, it took approximately 2 min for the equipment to track back to the animal's previous acuity level. The vertical bars around the data points represent ± 1 SD about the animal's mean acuity and demonstrate very little variance in the animal's performance under these conditions. Each data point represents the average of 4 - 6 different sham exposures presented over several weeks of testing. When the animal was exposed to laser irradiation, his derived acuity did not recover immediately but remained depressed before gradually returning to its pre-exposure level. In these instances, the variability across sessions was much larger indicating postexposure performances following laser irradiation were not as predictable as the animal's normal baseline acuity.

The viewing conditions under which the effects of the laser flash were assessed made a significant difference in the observed magnitude of both the initial deficit and subsequent time for recovery in those instances where recovery was observed. Furthermore, we have previously reported that when only achromatic targets are used to assess visual function, permanent shifts in postexposure acuity might exist if visual function were to be examined under different chromatic or contrast conditions. For this reason, during the course of this project we have examined postexposure recovery and acuity under a variety of viewing conditions.

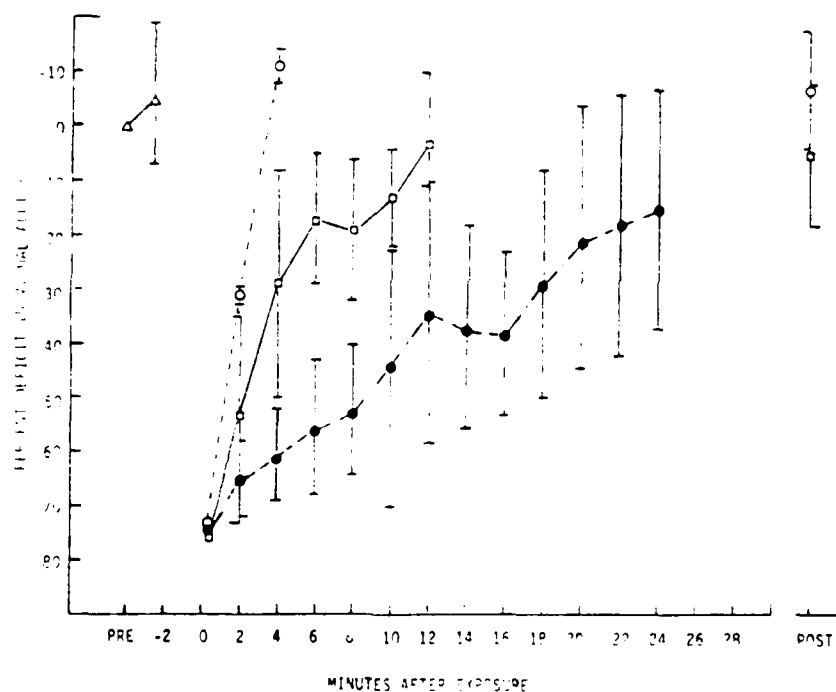


Figure 6. Recovery functions for one animal following 2.0 mW and 3.0 mW Argon (514.5 nm) flashes. Each data point represents the mean of 4 - 6 exposures. Only one exposure was made per day and a random design for power densities was employed. The open circles represent sham exposures where no laser flash was presented. The squares indicate recovery from 2.0 mW exposures and the dark circles recovery from 3.0 mW exposures. The vertical bars represent a variance of one standard deviation about the animal's mean acuity for that time period following exposure. Acuity was measured under maximum photopic conditions with a high contrast (97%) white light background.

Using monochromatic instead of white light backgrounds, pre- and immediate postexposure acuity was examined for 514.5 nm and 647 nm exposures. In Figure 7, one animal was exposed repeatedly to 2.0 mW exposures from an Argon laser over a period of several weeks. Consistent with all other exposures, only one, 100 msec flash was presented per day and postexposure acuity testing began immediately following the exposure and continued until full recovery was evident. The energy level employed was below that necessary to produce a permanent shift in postexposure acuity under this or any other viewing condition. The background contrast level was set at 90%. As can be seen in Figure 11, immediately following exposure, postexposure acuity decreased to approximately 70% of its pre-exposure level and remained

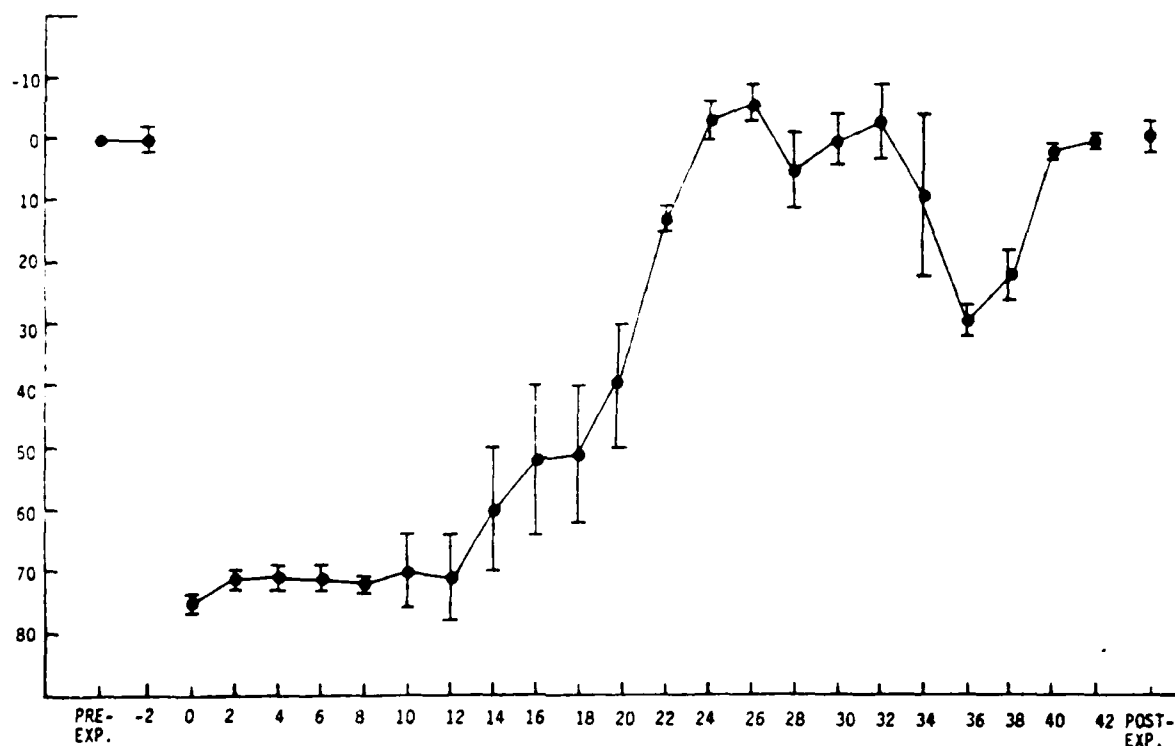


Figure 7. Recovery function for repetitive 2.0 mW Argon (514.5 nm) flashes when measured using a high contrast, chromatic (640 nm) background. Only one exposure was made per session and each data point represents the mean of 4-6 individual test sessions. The vertical bars represent ± 1 SD on either side of the mean value.

depressed at this level for 12 min before gradually returning to its pre-exposure level. In comparison to the achromatic recovery functions shown previously, the initial changes in acuity remained depressed for a longer period of time when monochromatic backgrounds were used which generally resulted in a longer time for full recovery than when achromatic backgrounds were employed. While the overall differences in recovery were small, these differences demonstrate the heightened ability of monochromatic backgrounds to detect changes in postexposure spatial resolution. Similar differences between achromatic and chromatic backgrounds were found in other animals using different exposure paradigms.

Immediate and long term postexposure acuity was also measured using targets on backgrounds of different contrast levels. These backgrounds were both achromatic and chromatic. As with different chromatic backgrounds, recovery functions derived using different background contrasts also affected

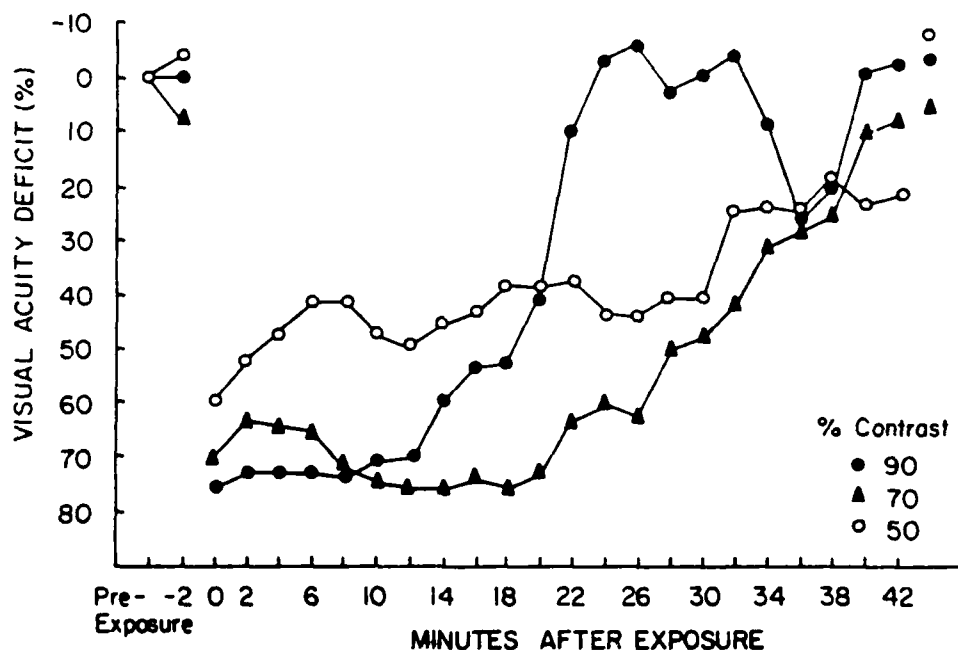


Figure 8. Effects of target contrast on amount and duration of acuity recovery following repeated exposures to Argon (514.5 nm) flashes. The diameter of the 2 mW flash on the retina was 50 microns. Three different contrast levels (50, 70 and 90%) were employed. The background of the darkened Landolt ring was 640 nm and each data point represents the average of several exposure sessions.

the amount and duration of any acuity deficit following laser irradiation. Unlike the case with chromatic targets, however, the magnitude of the initial deficit was affected by the specific contrast level employed. Sample recovery functions for one animal exposed under different contrast conditions is shown in Figure 8. In this example, the animal was exposed on separate occasions to 2 mW, 100 msec flashes from an Argon laser. Each recovery function is the animal's mean performance level for several exposure sessions. For high contrast targets (90%), postexposure acuity dropped immediately to 75% of its pre-exposure level and remained at this depressed level for approximately 18 min before quickly returning to its pre-exposure level in approximately 26 min. This curve is reminiscent of those shown in previous figures for other high contrast targets. For this condition, however, during the next twenty minutes the animal's postexposure acuity fluctuated more than normal although by the end of the session and 24 hr later, recovery was complete. When contrast levels were reduced, the magnitude of the initial deficit decreased from 75% to 60% of its pre-exposure level and the overall slope of the recovery functions declined progressively for lower contrast targets indicating a longer time for full recovery to occur. Furthermore, for the lowest contrast levels employed (50%), the animal's ability to maintain a consistent acuity level was reduced as reflected in a higher session variability for both pre- and postexposure acuity testing.

While the primary exposure variable manipulated in relation to the effects of laser irradiation on vision was the energy density of the flash, also examined was the position, size, and duration of the exposure on the retina. These changes, like that of exposure energy, also had a significant effect on the degree and time course of the recovery function in those cases where full recovery was possible. The effects of changes in the retinal spot size are shown in Figure 9. In this figure, the energy and duration of the

exposure as well as viewing conditions were held constant while the size of the laser spot on the retina was shifted from less than 50 microns (defined as a minimal diameter spot) to 323 microns and each was compared to a sham condition where no laser exposure occurred. These individual recovery functions represent the mean acuities and for clarity, indications of inter-

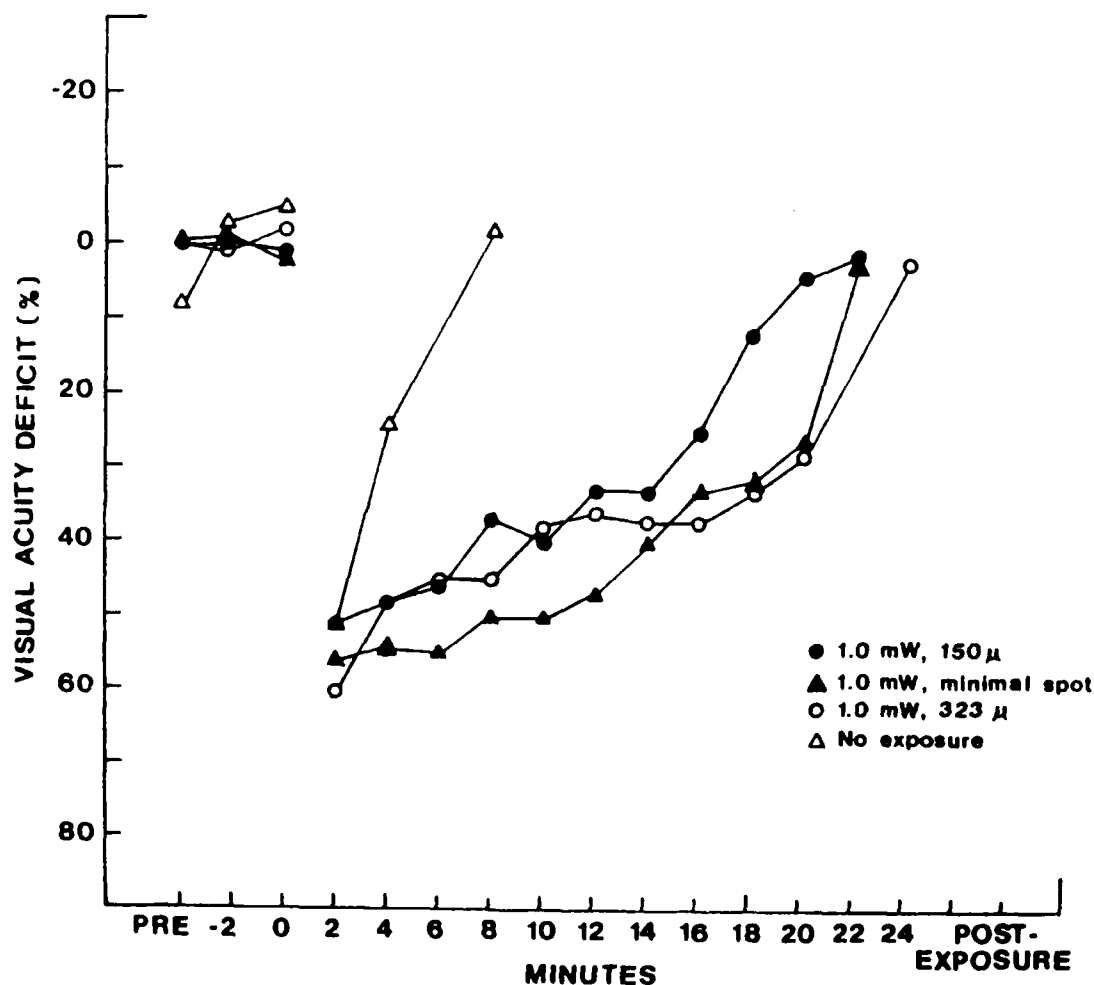


Figure 9. Effects of laser spot diameters on the magnitude and duration of visual deficits following repeated 1.0 mW Argon (514.5 nm) exposures. Each recovery curve was derived in similar manner following a 100 msec exposure positioned on the central fovea. The exposure energy of 1.0 mW was significantly below that which produced a permanent shift in postexposure acuity for this duration flash. Changes in retinal spot size were produced by changing the expanding telescope and final converging lens in the laser optical system. Acuity was measured using high contrast, achromatic backgrounds.

session variability, which was remarkably small, are not shown. Somewhat small also was the observed differences in the average recovery time when different diameter spots were employed. Within animals, the magnitude of the initial deficit was related to exposure diameter for the three conditions shown here (50, 150, 323 microns). For minimal diameter spots, the magnitude of the initial deficit was relatively smaller (40-50% range) while for larger diameter spots (323 microns) the average deficits ranged from 70% to 80% of pre-exposure acuity. For a given subject, the energy of the exposure had little influence on the magnitude of the initial deficit although, as mentioned elsewhere, the likelihood and the time course of recovery were significantly affected. The nature of the viewing conditions (contrast and color) also affected the magnitude of the elicited acuity deficit both in absolute and relative terms. It should be noted that the actual diameter of the laser spot on the retina was somewhat larger than indicated here since the animal's eye was in constant motion during the 100 msec flash. These irregular eye movements would have smeared the image across a larger than indicated retinal area although not allowed time enough for the subject to voluntarily change its point of fixation. Reducing the duration of the exposure below 100 msec might therefore have a significant effect on postexposure acuity especially when relatively small diameter spots are employed since the beam would be spread over a lesser area.

Figure 10 demonstrates the effects that variations in exposure duration can have on the duration of the recovery function when minimal diameter spots are employed. In this figure, the individual recovery functions for minimal diameter spots are shown for different durations of exposure ranging from 19 msec flashes to 103 msec (representing an average 100 msec flash). A minimal diameter laser beam which produced a retinal spot of 50 microns was employed.

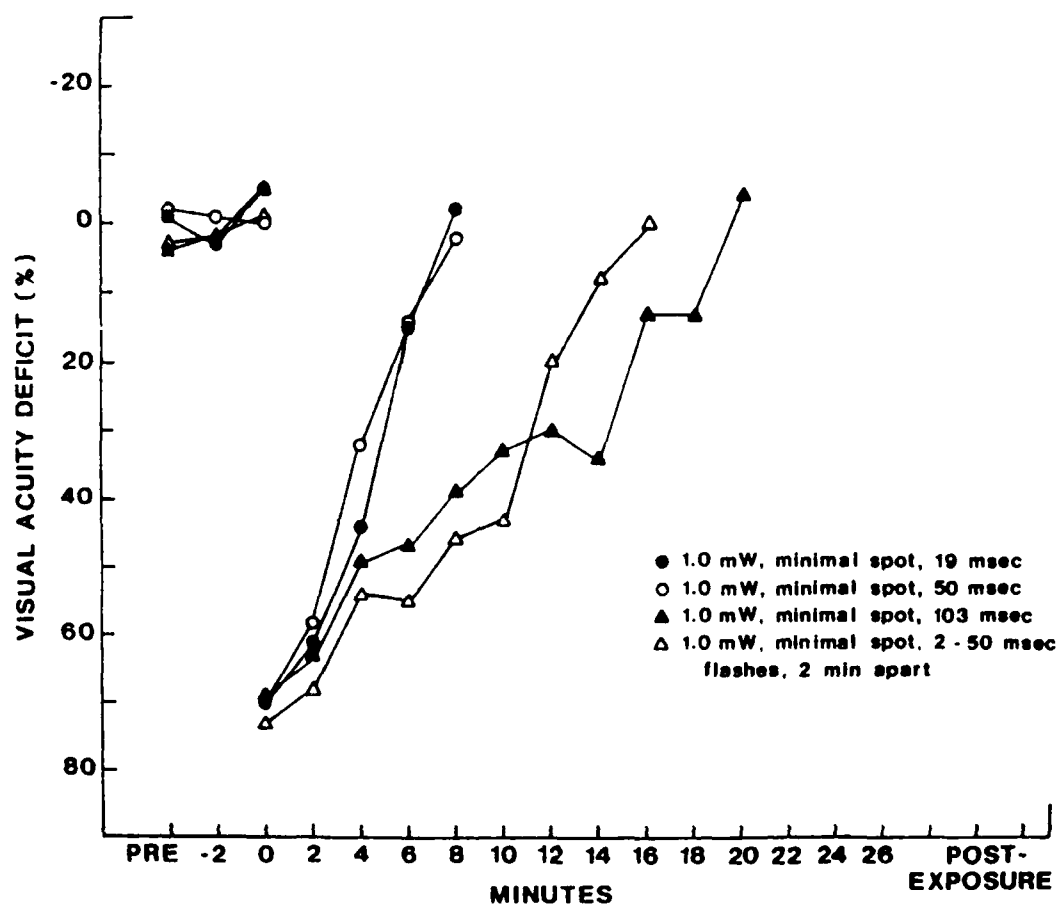


Figure 10. Effects of exposure duration on the post-exposure visual acuity for a minimal diameter, 1.0 mW Argon (514.5 nm) exposure. The individual recovery functions were derived from one animal exposed repeatedly to 1.0 mW flashes of approximately 50 microns in diameter on the retina. Visual acuity was tested using an achromatic, high contrast background. The data points represent the means of several different exposures. The durations of retinal exposure employed are shown in the lower right hand portion of the figure. Various durations were produced by a programmable electronic shutter whose pulse duration was measured on a standard storage oscilloscope.

As the figure shows, recovery to flashes of 19 msec and 50 msec are almost immediate (within 4 to 6 minutes) and represent recovery times not significantly different from the sham condition shown in Figures 6 and 9 (instances where no exposure was presented and instead the animal was allowed to track its artificially depressed acuity back to its previous level). For

the longer or repeated exposures, however, the duration of the recovery function for minimal diameter spots was similar to those observed when larger-diameter, retinal exposures were administered. It would appear from this data, that the consequences of one longer, 103 msec flash were slightly greater than two, 50 msec flashes presented 2 min apart. Such might be the case if eye movements alone were the prevailing catalyst for the effect.

Our data would appear to support the notion that the size of the area of involvement, whether as the result of beam diameter or exposure duration, has a significant effect on the magnitude and duration of any observed acuity deficit. In figure 11 the position of the beam was intentionally positioned away from the gap in the discriminanda and therefore away from the point of central fixation. Under this paradigm, as the position of the beam was placed increasingly off-axis, the duration of the recovery function decreased. When the minimal diameter, 100 msec flash was placed beyond 6 degrees off the point of central fixation, no long term shift in postexposure acuity was noted and the animal's behavior was identical to that of the sham exposure.

The previous figures have focused on the transient effects that relatively low energy laser irradiation has on immediate postexposure visual acuity. In these cases, full recovery was typically complete within the 45 min postexposure test session. When higher energy levels were employed, however, full recovery either was delayed for several days or impossible to achieve. In these cases, further exposures were postponed or suspended and complete analyses of postexposure sensitivity were made under a variety of viewing conditions. The laser energy level associated with a permanent functional change was defined as a threshold value for that particular viewing condition. Generally, the animal's postexposure visual sensitivity following a permanent functional alteration was followed for a period of 6 to 12 months.

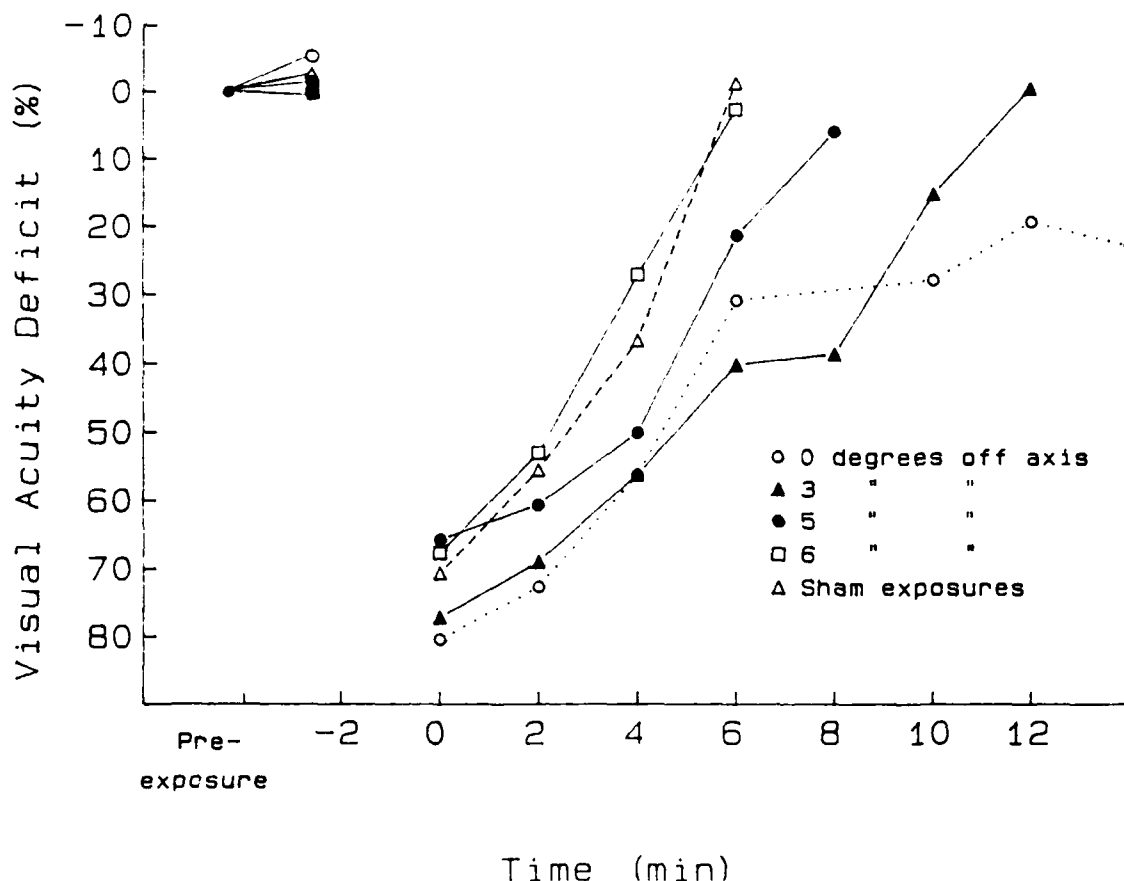


Figure 11. Recovery in visual acuity following 2.0 mW Krypton (647 nm) exposures at various eccentricities. This animal was exposed repeatedly to 100 msec flashes and postexposure acuity was measured using an achromatic background (70% contrast). The recovery curves and the exposure eccentricities employed are indicated.

Often, long term testing in the exposed eye produced greater day to day variability than the animal had previously shown even though no such differences were found in the unexposed eye which was also tested during this same time period. In Figure 12 changes in spectral acuity over several months is shown for another animal exposed to an Argon laser. Similar to other postexposure data, immediately following exposure (filled circles), the entire spectral acuity function was depressed. With time, recovery was observed in all spectral regions tested except the short wavelength region. Also shown are the changes in achromatic acuity for this same animal and after two months, achromatic acuity had fully recovered to its pre-exposure level.

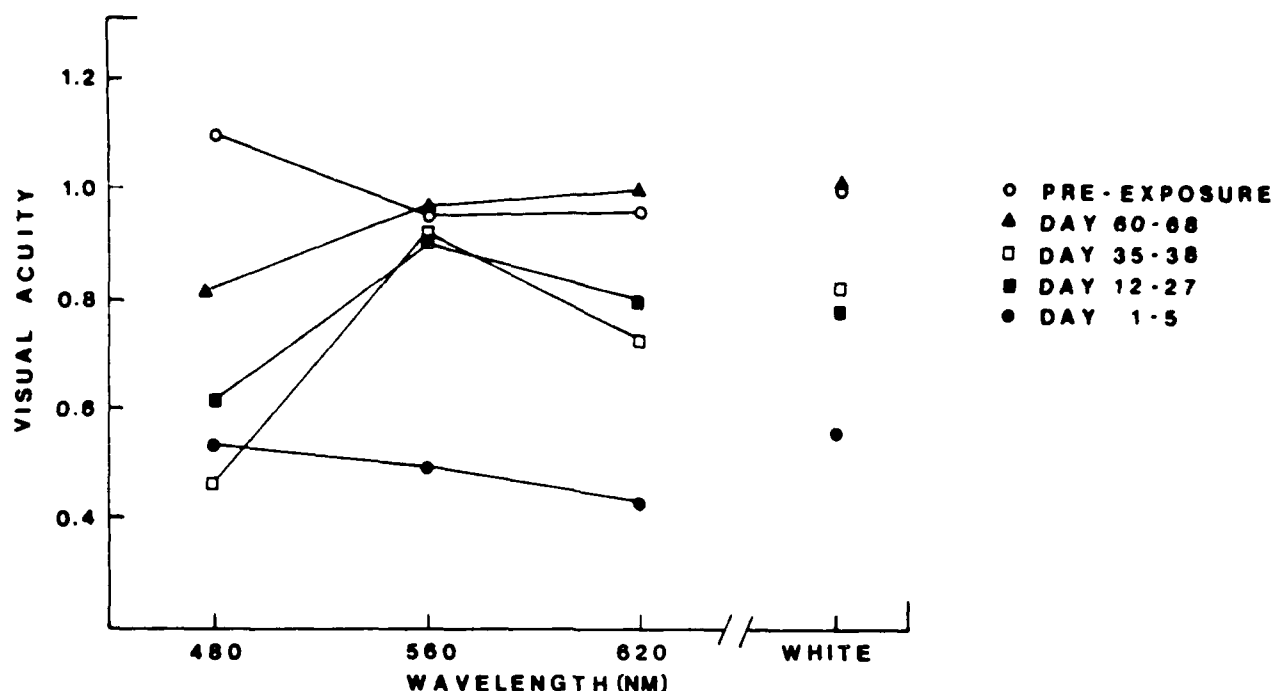


Figure 12. Changes in mean postexposure spectral acuity over several months of testing following exposure to a 100 msec, 3.0 mW Argon flash. Spectral acuity was defined as the acuity level achieved for darkened rings superimposed on different monochromatic backgrounds each equated for equal numbers of quanta. The overall luminance of the monochromatic backgrounds were equated to the achromatic backgrounds also used and were at a level which produced the maximum spectral and achromatic acuity. This acuity corresponded to a mean Snellen acuity of 20/18 for this animal. During this time period the maximum deficit produced for spectral acuity was 20/50 for 620 nm backgrounds and 20/34 for equated achromatic backgrounds. This animal was tested daily during the first two months of postexposure testing and each data point represents the mean acuity during the time period stated on the right hand portion of the figure. Other spectral backgrounds were also employed but are not shown here.

DISCUSSION

Our data continue to demonstrate that exposure of the fovea to a brief, isolated flash of coherent light produces an immediate, and significant shift

in visual acuity which, depending upon exposure energy, can last anywhere from several minutes to several years. In our study, the magnitude of the acuity deficit was related to the size of the retinal exposure while the duration time for full recovery, when possible, was a function of laser energy somewhat independent of spot size. Once exposed, our animals maintained vigil and continued to respond to Landolt rings provided the gap sizes were significantly larger in visual angle to accommodate the animal's decreased foveal vision. Our data suggest that our animals did not change their criterion for detection (beta value) of the critical feature in the Landolt ring, as indicated by their unchanged false alarm rate for targets below their new threshold level. What did change was the animal's sensitivity (d') to resolve this spatial task. The fact that laser exposures did not result in a total functional impairment implies that the animals quickly learned to employ alternative, unexposed retinal areas to make the required discrimination. Given the size of our exposing beam, these areas would normally be outside the foveal region, in areas where spatial resolution is reduced. The magnitude of the initial deficit and its dependence on beam diameter supports this parafoveal hypothesis. An alternative hypothesis, however, might be that laser exposure resulted in an incomplete saturation of the photoreceptors and the resultant acuity levels obtained represented the activity of nondepleted foveal photoreceptors. Recovery would then represent the time required for affected foveal photoreceptors to again become fully functional. If this hypothesis was correct, however, one would expect that both the magnitude and the duration of any elicited deficit in visual acuity would be dependent upon exposure energy. Our results clearly indicate that only recovery time was related to exposure energy suggesting that the former, parafoveal hypothesis, more accurately accounts for our observed visual deficits.

The relatively large deficits (50% to 90%) produced by even our minimal

diameter beams (50 micron spot on the retina) could be explained in terms of the influences of involuntary eye movements. Since our exposures typically were 100 msec in duration, the actual diameter of the laser spot on the retina was somewhat larger than indicated here since the animal's eye was in constant motion during the 100 msec flash. The relatively short duration of this flash did prevent the animal from voluntarily moving his eye away from the bright light source but the rapid, irregular involuntary eye movements naturally occurring during any fixation would have smeared the image across a larger than initially predicted area. This might explain why even relatively small diameter retinal exposures (50 microns) produced a somewhat larger and longer decrement in postexposure visual acuity than might otherwise be expected. Given the size of the central fovea and the small diameter of our minimal spot, one might expect not to observe any shift in postexposure acuity with this type of irradiation since the animal should still be able to use unexposed regions of the fovea to make the required visual discrimination. Reducing the duration of the exposure below 100 msec might therefore produce no significant deficit in postexposure acuity especially when relatively small diameter spots are employed. Increasing the exposure duration above 100 msec, on the other hand, might be expected to have no greater effect over those previously observed since, for these longer durations, the animal's voluntary gaze away from the spot would reduce its foveal consequences. In our studies, very short duration exposures (<50 msec) produce little or no observed temporary deficits in visual acuity for those energy levels that were below the ED₅₀ level.

The notion that the size of the area of foveal involvement, whether as the result of beam diameter or exposure duration, has a significant effect on the magnitude and duration of any observed acuity deficit, was also supported by our off-axis experiments. As previously mentioned, larger beam diameters

or longer duration exposures might be expected to involve increasingly larger areas of the central fovea and therefore produce even greater deficits in photopic acuity. In this paradigm the laser beam was intentionally positioned away from the animal's point of central fixation (off-axis). As might be expected, depending upon the degree of eccentricity, the magnitude and duration of the elicited visual acuity deficits decreased as the beam exposed more peripheral retinal areas. These results would suggest that under normal exposure conditions, our paradigm reliably produced placements of the laser beam on the central fovea and that our detection task was a reliable measure of functional changes that coincide with such exposures.

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